



Clinical trial results:

A Dose-Blind Extension Study With Double-blind, Placebo-Controlled, Randomized Withdrawal Period to Evaluate the Safety and Explore the Pharmacokinetics and Pharmacodynamics of TAK-994 in Adults With Narcolepsy With Cataplexy (Narcolepsy Type 1)

Summary

EudraCT number	2021-000251-39
Trial protocol	CZ HU FR IT ES
Global end of trial date	03 November 2021

Results information

Result version number	v2 (current)
This version publication date	19 November 2023
First version publication date	15 December 2022
Version creation reason	
Summary attachment (see zip file)	TAK-994-1504_2021-000251-39_EudraCT PDF (TAK-994-1504_2021-000251-39_EudraCT PDF_revised.pdf)

Trial information

Trial identification

Sponsor protocol code	TAK-994-1504
-----------------------	--------------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04820842
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Takeda
Sponsor organisation address	95 Hayden Avenue, Lexington, United States, MA 02421
Public contact	Study Director, Takeda, TrialDisclosures@takeda.com
Scientific contact	Study Director, Takeda, TrialDisclosures@takeda.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	03 November 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	03 November 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to evaluate the safety and tolerability of TAK-994 in the Active Drug Extension Period of the study over a period of up to 8 weeks.

Protection of trial subjects:

Each participant signed an informed consent form before participating in the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 April 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Italy: 9
Country: Number of subjects enrolled	Japan: 2
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	Korea, Republic of: 1
Country: Number of subjects enrolled	United States: 9
Worldwide total number of subjects	26
EEA total number of subjects	14

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	26
From 65 to 84 years	0

85 years and over	0
-------------------	---

Subject disposition

Recruitment

Recruitment details:

Participants took part in study at 13 investigative sites in Spain,Italy,Japan,Korea,United States from 30Apr2021-29Jun2022[LPLV].Study officially terminated in Nov2021,however,database lock and full data analysis significantly delayed as participants with serious hepatic safety events were being followed,respective data collected until Jun2022.

Pre-assignment

Screening details:

Participants with narcolepsy type 1 (NT 1) who completed Part B of TAK-994-1501(NCT04096560) were enrolled in this study to receive TAK-994 or placebo.

Period 1

Period 1 title	Active Drug Extension Period (8 Weeks)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Active Drug Extension Period: TAK-99430 mg

Arm description:

TAK-994 30 mg, twice daily (BID) tablets, orally, from Day 1 (Day 57 of previous study) to Day 56 in the Active Drug Extension Period.

Arm type	Experimental
Investigational medicinal product name	TAK-994
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

TAK-994 tablet, was administered orally, from Day 1 (Day 57 of previous study) to Day 56.

Arm title	Active Drug Extension Period: TAK-994 90 mg
------------------	---

Arm description:

TAK-994 90 mg, BID, tablets, orally, from Day 1 (Day 57 of previous study) to Day 56 in the Active Drug Extension Period.

Arm type	Experimental
Investigational medicinal product name	TAK-994
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

TAK-994 tablet, was administered orally, from Day 1 (Day 57 of previous study) to Day 56.

Arm title	Active Drug Extension Period: TAK-994 180 mg
------------------	--

Arm description:

TAK-994 180 mg, BID, tablets, orally, from Day 1 (Day 57 of previous study) to Day 56 in the Active Drug Extension Period.

Arm type	Experimental
----------	--------------

Investigational medicinal product name	TAK-994
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

TAK-994 tablet, was administered orally, from Day 1 (Day 57 of previous study) to Day 56.

Number of subjects in period 1	Active Drug Extension Period: TAK-99430 mg	Active Drug Extension Period: TAK-994 90 mg	Active Drug Extension Period: TAK-994 180 mg
Started	8	9	9
Completed	5	1	2
Not completed	3	8	7
Consent withdrawn by subject	-	1	-
Adverse event, non-fatal	-	1	2
Study Terminated by Sponsor	3	6	5

Period 2

Period 2 title	Randomized Withdrawal Period (4 Weeks)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Double-blind Randomized Withdrawal Period: TAK-994 30 mg

Arm description:

Following the Active Drug Extension Period, participants randomized to active treatment 30 mg, BID, meeting eligibility specification and continued to receive same dose (TAK-994, 30 mg, BID, tablets, orally) from Day 57 to Day 84 in the Double-blind Randomized Withdrawal Period.

Arm type	Experimental
Investigational medicinal product name	TAK-994
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

TAK-994 tablet, was administered orally, from Day 57 to Day 84.

Arm title	Double-blind Randomized Withdrawal Period: TAK-994 90 mg
------------------	--

Arm description:

Following the Active Drug Extension Period, participants randomized to active treatment 90 mg, BID, meeting eligibility specification and continued to receive same dose (TAK-994, 90 mg, BID, tablets, orally) from Day 57 to Day 84 in the Double-blind Randomized Withdrawal Period.

Arm type	Experimental
Investigational medicinal product name	TAK-994
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

TAK-994 tablet, was administered orally, from Day 57 to Day 84.

Arm title	Double-blind Randomized Withdrawal Period: TAK-994 180 mg
------------------	--

Arm description:

Following the Active Drug Extension Period, participants randomized to active treatment 180 mg, BID, meeting eligibility specification and continued to receive same dose (TAK-994, 180 mg, BID, tablets, orally) from Day 57 to Day 84 in the Double-blind Randomized Withdrawal Period.

Arm type	Experimental
Investigational medicinal product name	TAK-994
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

TAK-994 tablet, was administered orally, from Day 57 to Day 84.

Arm title	Double-blind Randomized Withdrawal Period: Placebo
------------------	--

Arm description:

Following the Active Drug Extension Period participants meeting eligibility specification and received placebo-matching tablets for 4 weeks (from Day 57 to Day 84) in the Double-blind Randomized Withdrawal Period.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

TAK-994 placebo-matching tablet, was administered orally, for 4 weeks (from Day 57 to Day 84).

Number of subjects in period 2	Double-blind Randomized Withdrawal Period: TAK-994 30 mg	Double-blind Randomized Withdrawal Period: TAK-994 90 mg	Double-blind Randomized Withdrawal Period: TAK-994 180 mg
Started	3	1	1
Completed	1	1	1
Not completed	2	0	0
Study Terminated by Sponsor	2	-	-

Number of subjects in period 2	Double-blind Randomized Withdrawal Period: Placebo
Started	3

Completed	2
Not completed	1
Study Terminated by Sponsor	1

Baseline characteristics

Reporting groups

Reporting group title	Active Drug Extension Period: TAK-99430 mg
Reporting group description: TAK-994 30 mg, twice daily (BID) tablets, orally, from Day 1 (Day 57 of previous study) to Day 56 in the Active Drug Extension Period.	
Reporting group title	Active Drug Extension Period: TAK-994 90 mg
Reporting group description: TAK-994 90 mg, BID, tablets, orally, from Day 1 (Day 57 of previous study) to Day 56 in the Active Drug Extension Period.	
Reporting group title	Active Drug Extension Period: TAK-994 180 mg
Reporting group description: TAK-994 180 mg, BID, tablets, orally, from Day 1 (Day 57 of previous study) to Day 56 in the Active Drug Extension Period.	

Reporting group values	Active Drug Extension Period: TAK-99430 mg	Active Drug Extension Period: TAK-994 90 mg	Active Drug Extension Period: TAK-994 180 mg
Number of subjects	8	9	9
Age Categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	31.4 ± 12.13	31.3 ± 9.75	29.7 ± 11.08
Gender categorical Units: Subjects			
Female	7	4	3
Male	1	5	6
Ethnicity Units: Subjects			
Hispanic or Latino	1	0	0
Not Hispanic or Latino	7	9	9
Unknown or Not Reported	0	0	0
Race Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	1	1	1
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	2	1
White	6	6	6
More than one race	1	0	0
Unknown or Not Reported	0	0	1
Region of Enrollment Units: Subjects			
Spain	4	1	0
Italy	1	4	4
Japan	1	0	1

Korea, South	0	1	0
United States	2	3	4

Height			
Units: centimeters (cm)			
arithmetic mean	163.9	170.5	174.4
standard deviation	± 8.39	± 8.24	± 6.45
Body Mass Index (BMI)			
BMI=weight (kg) / [height (m)]^2			
Units: kilograms per meter square (kg/m^2)			
arithmetic mean	28.3	27.7	25.9
standard deviation	± 5.86	± 5.45	± 5.07
Weight			
Units: kilograms (kg)			
arithmetic mean	76.5	81.8	79.1
standard deviation	± 18.52	± 22.68	± 16.15

Reporting group values	Total		
Number of subjects	26		
Age Categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	14		
Male	12		
Ethnicity			
Units: Subjects			
Hispanic or Latino	1		
Not Hispanic or Latino	25		
Unknown or Not Reported	0		
Race			
Units: Subjects			
American Indian or Alaska Native	0		
Asian	3		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	3		
White	18		
More than one race	1		
Unknown or Not Reported	1		
Region of Enrollment			
Units: Subjects			
Spain	5		
Italy	9		
Japan	2		
Korea, South	1		

United States	9		
Height			
Units: centimeters (cm)			
arithmetic mean			
standard deviation	-		
Body Mass Index (BMI)			
BMI=weight (kg) / [height (m)]^2			
Units: kilograms per meter square (kg/m^2)			
arithmetic mean			
standard deviation	-		
Weight			
Units: kilograms (kg)			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups

Reporting group title	Active Drug Extension Period: TAK-99430 mg
Reporting group description: TAK-994 30 mg, twice daily (BID) tablets, orally, from Day 1 (Day 57 of previous study) to Day 56 in the Active Drug Extension Period.	
Reporting group title	Active Drug Extension Period: TAK-994 90 mg
Reporting group description: TAK-994 90 mg, BID, tablets, orally, from Day 1 (Day 57 of previous study) to Day 56 in the Active Drug Extension Period.	
Reporting group title	Active Drug Extension Period: TAK-994 180 mg
Reporting group description: TAK-994 180 mg, BID, tablets, orally, from Day 1 (Day 57 of previous study) to Day 56 in the Active Drug Extension Period.	
Reporting group title	Double-blind Randomized Withdrawal Period: TAK-994 30 mg
Reporting group description: Following the Active Drug Extension Period, participants randomized to active treatment 30 mg, BID, meeting eligibility specification and continued to receive same dose (TAK-994, 30 mg, BID, tablets, orally) from Day 57 to Day 84 in the Double-blind Randomized Withdrawal Period.	
Reporting group title	Double-blind Randomized Withdrawal Period: TAK-994 90 mg
Reporting group description: Following the Active Drug Extension Period, participants randomized to active treatment 90 mg, BID, meeting eligibility specification and continued to receive same dose (TAK-994, 90 mg, BID, tablets, orally) from Day 57 to Day 84 in the Double-blind Randomized Withdrawal Period.	
Reporting group title	Double-blind Randomized Withdrawal Period: TAK-994 180 mg
Reporting group description: Following the Active Drug Extension Period, participants randomized to active treatment 180 mg, BID, meeting eligibility specification and continued to receive same dose (TAK-994, 180 mg, BID, tablets, orally) from Day 57 to Day 84 in the Double-blind Randomized Withdrawal Period.	
Reporting group title	Double-blind Randomized Withdrawal Period: Placebo
Reporting group description: Following the Active Drug Extension Period participants meeting eligibility specification and received placebo-matching tablets for 4 weeks (from Day 57 to Day 84) in the Double-blind Randomized Withdrawal Period.	

Primary: Number of Participants with at Least One Treatment Emergent Adverse Event (TEAE) During the Active Drug Extension Period

End point title	Number of Participants with at Least One Treatment Emergent Adverse Event (TEAE) During the Active Drug Extension Period ^[1]
End point description: An adverse event (AE) is defined as any untoward medical occurrence in a clinical investigation participants administered a drug; it does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (example, a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug whether or not it is considered related to the drug. A TEAE is defined as an AE with an onset that occurs after receiving study drug. Safety Analysis Set for the Active Drug Extension Period included all participants who were randomized and received at least 1 dose of study drug in the Active Drug Extension Period.	
End point type	Primary
End point timeframe: Up to 8 weeks in the Active Drug Extension Period (Weeks 1 to 8)	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive statistics were planned to be analysed for this endpoint.

End point values	Active Drug Extension Period: TAK-99430 mg	Active Drug Extension Period: TAK-994 90 mg	Active Drug Extension Period: TAK-994 180 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	9	9	
Units: participants	5	4	3	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants with at Least One Post-dose Markedly Abnormal Value (MAV) in Laboratory Test During the Active Drug Extension Period

End point title	Number of Participants with at Least One Post-dose Markedly Abnormal Value (MAV) in Laboratory Test During the Active Drug Extension Period ^[2]
-----------------	--

End point description:

Clinical laboratory tests included hematology, serum chemistry, urinalysis. MAV criteria: Hemoglobin < 0.8 × lower limit of normal (LLN), > 1.2 × upper limit of normal (ULN); Hematocrit < 0.8 × LLN, > 1.2 × ULN; Red blood cells (RBC) count < 0.8 × LLN, > 1.2 × ULN; White blood cells (WBC) count < 0.5 × LLN, > 1.5 × ULN; Platelet count < 75 × 10⁹/liter (L), > 600 × 10⁹/L; alanine aminotransferase (ALT) > 3 × ULN; aspartate aminotransferase (AST) > 3 × ULN; gamma-glutamyl transferase (GGT) > 3 × ULN; Alkaline phosphatase > 3 × ULN; Total bilirubin > 1.5 × ULN; Albumin < 25 grams per liter (g/L); Total protein < 0.8 × LLN, > 1.2 × ULN; Creatinine > 1.5 × ULN; Blood urea nitrogen > 40 milligrams per deciliters (mg/dL); Sodium < 130 milliequivalents per liter (mEq/L), > 150 mEq/L; Potassium < 3.0 millimoles per liter (mmol/L), > 5.3 mmol/L; creatine phosphokinase (CPK) > 3 × ULN; Glucose < 50 mg/dL, > 300 mg/dL; Calcium < 7.7 mg/dL, > 11.1 mg/dL. Only categories with at least 1 participant with event are reported. Safety Analysis Set = all randomized participants who received at least 1 dose of study drug.

End point type	Primary
----------------	---------

End point timeframe:

Up to 8 weeks in the Active Drug Extension Period (Weeks 1 to 8)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive statistics were planned to be analysed for this endpoint.

End point values	Active Drug Extension Period: TAK-99430 mg	Active Drug Extension Period: TAK-994 90 mg	Active Drug Extension Period: TAK-994 180 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	9	9	
Units: participants				
ALT: > 3 × ULN	0	1	2	
AST: > 3 × ULN	0	1	2	
Bilirubin: > 1.5 × ULN	0	1	1	
GGT: > 3 × ULN	0	1	0	
Potassium: > 5.3 mmol/L	0	0	1	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants with at Least One Post-dose MAV for Vital Signs During the Active Drug Extension Period

End point title	Number of Participants with at Least One Post-dose MAV for Vital Signs During the Active Drug Extension Period ^[3]
-----------------	---

End point description:

MAV criteria for vital signs were: Pulse <40 beats per minute (bpm), >115 bpm; Systolic blood pressure <90 millimeters of mercury (mmHg), ≥160 mmHg; Diastolic blood pressure <50 mmHg, ≥100 mmHg, Systolic or Diastolic blood pressure change of >20, >30 mmHg from Baseline, Body temperature >38.5 degree Celsius, Respiratory Rate >21 breath/minute. Only categories with at least one participant with event are reported. Baseline for this outcome measure is Day 1 of the Active Drug Extension Period.

End point type	Primary
----------------	---------

End point timeframe:

Up to 8 weeks in the Active Drug Extension Period (Weeks 1 to 8)

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive statistics were planned to be analysed for this endpoint.

End point values	Active Drug Extension Period: TAK-99430 mg	Active Drug Extension Period: TAK-994 90 mg	Active Drug Extension Period: TAK-994 180 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	9	9	
Units: participants				
Systolic Blood Pressure: <90 mmHg	0	1	0	
Systolic Blood Pressure: ≥160 mmHg	0	1	0	
Systolic Blood Pressure: Change from Pre-Dose >20	1	1	0	
Systolic Blood Pressure: Change from Pre-Dose >30	0	1	0	
Diastolic Blood Pressure: ≥100 mmHg	0	1	0	
Diastolic Blood Pressure: Change from Pre-Dose >20	2	1	1	
Diastolic Blood Pressure: Change from Pre-Dose >30	0	1	0	
Respiratory Rate: >21 breaths/min	1	0	2	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants with at Least One Post-dose MAV for

Electrocardiogram (ECG) Parameters During the Active Drug Extension Period

End point title	Number of Participants with at Least One Post-dose MAV for Electrocardiogram (ECG) Parameters During the Active Drug Extension Period ^[4]
-----------------	--

End point description:

MAV criteria for ECG were: Heart rate <40 bpm, >115 bpm; PR interval ≤80 milliseconds (msec), ≥200 msec; QT interval with Fridericia correction method (QTcF) Interval ≤300 msec, >500 msec or ≥30 msec change from baseline and >450 msec; QRS duration ≤80 msec, ≥180 msec. Only categories with at least one participant with event are reported. Safety Analysis Set for the Active Drug Extension Period included all participants who were randomized and received at least 1 dose of study drug in the Active Drug Extension Period.

End point type	Primary
----------------	---------

End point timeframe:

Up to 8 weeks in the Active Drug Extension Period (Weeks 1 to 8)

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive statistics were planned to be analysed for this endpoint.

End point values	Active Drug Extension Period: TAK-99430 mg	Active Drug Extension Period: TAK-994 90 mg	Active Drug Extension Period: TAK-994 180 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	9	9	
Units: participants				
Heart Rate: <40 bpm	1	0	1	
PR Interval: ≥200 msec	0	1	2	
QRS Duration: ≤80 msec	3	3	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with at Least One TEAE During the Double-blind Randomized Withdrawal Period

End point title	Number of Participants with at Least One TEAE During the Double-blind Randomized Withdrawal Period
-----------------	--

End point description:

An AE is defined as any untoward medical occurrence in a clinical investigation participants administered a drug; it does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (example, a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug whether or not it is considered related to the drug. A TEAE is defined as an AE with an onset that occurs after receiving study drug. Safety Analysis Set for the Double-blind Randomized Withdrawal Period included all participants who were randomized and received at least 1 dose of study drug in the Double-blind Randomized Withdrawal Period.

End point type	Secondary
----------------	-----------

End point timeframe:

Up to 4 weeks in the Double-blind Randomized Withdrawal Period (Weeks 9 to 12)

End point values	Double-blind Randomized Withdrawal Period: TAK-994 30 mg	Double-blind Randomized Withdrawal Period: TAK-994 90 mg	Double-blind Randomized Withdrawal Period: TAK-994 180 mg	Double-blind Randomized Withdrawal Period: Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	1	1	3
Units: participants	0	1	0	1

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with at Least One Post-dose MAV in Laboratory Test During the Double-blind Randomized Withdrawal Period

End point title	Number of Participants with at Least One Post-dose MAV in Laboratory Test During the Double-blind Randomized Withdrawal Period
-----------------	--

End point description:

Clinical laboratory tests included hematology, serum chemistry, and urinalysis. MAV criteria: Hemoglobin $<0.8 \times \text{LLN}$, $>1.2 \times \text{ULN}$; Hematocrit $<0.8 \times \text{LLN}$, $>1.2 \times \text{ULN}$; RBC count $<0.8 \times \text{LLN}$, $>1.2 \times \text{ULN}$; WBC count $<0.5 \times \text{LLN}$, $>1.5 \times \text{ULN}$; Platelet count $<75 \times 10^9/\text{L}$, $>600 \times 10^9/\text{L}$; ALT $>3 \times \text{ULN}$; AST $>3 \times \text{ULN}$; GGT $>3 \times \text{ULN}$; Alkaline phosphatase $>3 \times \text{ULN}$; Total bilirubin $>1.5 \times \text{ULN}$; Albumin $<25 \text{ g/L}$; Total protein $<0.8 \times \text{LLN}$, $>1.2 \times \text{ULN}$; Creatinine $>1.5 \times \text{ULN}$; Blood urea nitrogen $>40 \text{ mg/dL}$; Sodium $<130 \text{ mEq/L}$, $>150 \text{ mEq/L}$; Potassium $<3.0 \text{ mmol/L}$, $>5.3 \text{ mmol/L}$; CPK $>3 \times \text{ULN}$; Glucose $<50 \text{ mg/dL}$, $>300 \text{ mg/dL}$; Calcium $<7.7 \text{ mg/dL}$, $>11.1 \text{ mg/dL}$. Safety Analysis Set for the Double-blind Randomized Withdrawal Period included all participants who were randomized and received at least 1 dose of study drug in the Double-blind Randomized Withdrawal Period.

End point type	Secondary
----------------	-----------

End point timeframe:

Up to 4 weeks in the Double-blind Randomized Withdrawal Period (Weeks 9 to 12)

End point values	Double-blind Randomized Withdrawal Period: TAK-994 30 mg	Double-blind Randomized Withdrawal Period: TAK-994 90 mg	Double-blind Randomized Withdrawal Period: TAK-994 180 mg	Double-blind Randomized Withdrawal Period: Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	1	1	3
Units: participants	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with at Least One Post-dose MAV for Vital Signs During the Double-blind Randomized Withdrawal Period

End point title	Number of Participants with at Least One Post-dose MAV for Vital Signs During the Double-blind Randomized Withdrawal Period
-----------------	---

End point description:

MAV criteria for vital signs were: Pulse <40 bpm, >115 bpm; Systolic blood pressure <90 mmHg, ≥160 mmHg; Diastolic blood pressure <50 mmHg, ≥100 mmHg, Systolic or Diastolic blood pressure change of >20, >30 mmHg from Baseline, Body temperature >38.5 degree Celsius, Respiratory Rate >21 breath/minute. Only categories with at least one participant with event are reported. Baseline for this outcome measure is Day 1 of the Double-blind Randomized Withdrawal Period (Day 57 of this study). Safety Analysis Set for the Double-blind Randomized Withdrawal Period included all participants who were randomized and received at least 1 dose of study drug in the Double-blind Randomized Withdrawal Period.

End point type	Secondary
----------------	-----------

End point timeframe:

Up to 4 weeks in the Double-blind Randomized Withdrawal Period (Weeks 9 to 12)

End point values	Double-blind Randomized Withdrawal Period: TAK-994 30 mg	Double-blind Randomized Withdrawal Period: TAK-994 90 mg	Double-blind Randomized Withdrawal Period: TAK-994 180 mg	Double-blind Randomized Withdrawal Period: Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	1	1	3
Units: participants				
Systolic Blood Pressure: <90 mmHg	0	0	0	1
Systolic Blood Pressure: Change from Baseline >20	1	0	0	0
Diastolic Blood Pressure: Change from Baseline >20	1	1	0	1

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with at Least One Post-dose MAV for ECG Parameters During the Double-blind Randomized Withdrawal Period

End point title	Number of Participants with at Least One Post-dose MAV for ECG Parameters During the Double-blind Randomized Withdrawal Period
-----------------	--

End point description:

MAV criteria for ECG were: Heart rate <40 bpm, >115 bpm; PR interval ≤80 msec, ≥200 msec; QTcF Interval ≤300 msec, >500 msec or ≥30 msec change from baseline and >450 msec; QRS duration ≤80 msec, ≥180 msec. Only categories with at least one participant with event are reported. Safety Analysis Set for the Double-blind Randomized Withdrawal Period included all participants who were randomized and received at least 1 dose of study drug in the Double-blind Randomized Withdrawal Period.

End point type	Secondary
----------------	-----------

End point timeframe:

Up to 4 weeks in the Double-blind Randomized Withdrawal Period (Weeks 9 to 12)

End point values	Double-blind Randomized Withdrawal Period: TAK- 994 30 mg	Double-blind Randomized Withdrawal Period: TAK- 994 90 mg	Double-blind Randomized Withdrawal Period: TAK- 994 180 mg	Double-blind Randomized Withdrawal Period: Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	1	1	3
Units: participants				
QRS Duration ≤80 msec	0	0	0	1
Heart Rate <40 bpm	0	0	1	0

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From randomization up to two weeks post end of treatment (up to Week 14)

Adverse event reporting additional description:

Safety Analysis Set for the Active Drug Extension Period and Double-blind Randomized Withdrawal Period included all participants who were randomized and received at least 1 dose of study drug in the Active Drug Extension Period and Double-blind Randomized Withdrawal Period respectively.

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	24.0
--------------------	------

Reporting groups

Reporting group title	Period 1: TAK-994 30 mg BID
-----------------------	-----------------------------

Reporting group description:

TAK-994 30 mg, BID tablets, orally, from Day 1 (Day 57 of previous study) to Day 56 in the Active Drug Extension Period.

Reporting group title	Period 1: TAK-994 90 mg BID
-----------------------	-----------------------------

Reporting group description:

TAK-994 90 mg, BID, tablets, orally, from Day 1 (Day 57 of previous study) to Day 56 in the Active Drug Extension Period.

Reporting group title	Period 1: TAK-994 180 mg BID
-----------------------	------------------------------

Reporting group description:

TAK-994 180 mg, BID, tablets, orally, from Day 1 (Day 57 of previous study) to Day 56 in the Active Drug Extension Period.

Reporting group title	Period 2: Placebo
-----------------------	-------------------

Reporting group description:

Following the Active Drug Extension Period participants meeting eligibility specification and received placebo-matching tablets for 4 weeks (from Day 57 to Day 84) in the Double-blind Randomized Withdrawal Period.

Reporting group title	Period 2: TAK-994 90 mg BID
-----------------------	-----------------------------

Reporting group description:

Following the Active Drug Extension Period, participants randomized to active treatment 90 mg, BID, meeting eligibility specification and continued to receive same dose (TAK-994, 90 mg, BID, tablets, orally) from Day 57 to Day 84 in the Double-blind Randomized Withdrawal Period.

Reporting group title	Period 2: TAK-994 180 mg BID
-----------------------	------------------------------

Reporting group description:

Following the Active Drug Extension Period, participants randomized to active treatment 180 mg, BID, meeting eligibility specification and continued to receive same dose (TAK-994, 180 mg, BID, tablets, orally) from Day 57 to Day 84 in the Double-blind Randomized Withdrawal Period.

Reporting group title	Period 2: TAK-994 30 mg BID
-----------------------	-----------------------------

Reporting group description:

Following the Active Drug Extension Period, participants randomized to active treatment 30 mg, BID, meeting eligibility specification and continued to receive same dose (TAK-994, 30 mg, BID, tablets, orally) from Day 57 to Day 84 in the Double-blind Randomized Withdrawal Period.

Serious adverse events	Period 1: TAK-994 30 mg BID	Period 1: TAK-994 90 mg BID	Period 1: TAK-994 180 mg BID
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	1 / 9 (11.11%)

number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Hepatobiliary disorders			
Hepatitis acute			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Period 2: Placebo	Period 2: TAK-994 90 mg BID	Period 2: TAK-994 180 mg BID
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 3 (0.00%)	0 / 1 (0.00%)	0 / 1 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Hepatobiliary disorders			
Hepatitis acute			
subjects affected / exposed	0 / 3 (0.00%)	0 / 1 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 1 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Period 2: TAK-994 30 mg BID		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 3 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Hepatobiliary disorders			
Hepatitis acute			

subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatitis			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Period 1: TAK-994 30 mg BID	Period 1: TAK-994 90 mg BID	Period 1: TAK-994 180 mg BID
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 8 (62.50%)	4 / 9 (44.44%)	3 / 9 (33.33%)
General disorders and administration site conditions			
Temperature intolerance			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Nervousness			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Investigations			
Blood pressure increased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Aspartate aminotransferase increased			

subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 9 (0.00%) 0	2 / 9 (22.22%) 2
Hepatic enzyme increased subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 9 (0.00%) 0	0 / 9 (0.00%) 0
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 9 (0.00%) 0	0 / 9 (0.00%) 0
Headache subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 9 (0.00%) 0	1 / 9 (11.11%) 1
Migraine subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	0 / 9 (0.00%) 0	0 / 9 (0.00%) 0
Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 9 (11.11%) 1	0 / 9 (0.00%) 0
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	0 / 9 (0.00%) 0	0 / 9 (0.00%) 0
Dry mouth subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	0 / 9 (0.00%) 0	0 / 9 (0.00%) 0
Hepatobiliary disorders Hepatic steatosis subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 9 (11.11%) 1	0 / 9 (0.00%) 0
Skin and subcutaneous tissue disorders Urticaria subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 9 (11.11%) 1	0 / 9 (0.00%) 0
Renal and urinary disorders Pollakiuria			

subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	1 / 9 (11.11%) 1	1 / 9 (11.11%) 1
Micturition urgency subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 9 (0.00%) 0	1 / 9 (11.11%) 1
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	0 / 9 (0.00%) 0	0 / 9 (0.00%) 0
Back pain subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 9 (11.11%) 1	0 / 9 (0.00%) 0
Infections and infestations			
Nasopharyngitis subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 9 (11.11%) 1	0 / 9 (0.00%) 0
Upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	1 / 9 (11.11%) 1	0 / 9 (0.00%) 0
Oral herpes subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	0 / 9 (0.00%) 0	0 / 9 (0.00%) 0
Conjunctivitis subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	0 / 9 (0.00%) 0	0 / 9 (0.00%) 0
Metabolism and nutrition disorders			
Vitamin D deficiency subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 9 (0.00%) 0	1 / 9 (11.11%) 1
Diabetes mellitus subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 9 (0.00%) 0	1 / 9 (11.11%) 1

Non-serious adverse events	Period 2: Placebo	Period 2: TAK-994 90 mg BID	Period 2: TAK-994 180 mg BID
Total subjects affected by non-serious adverse events subjects affected / exposed	1 / 3 (33.33%)	1 / 1 (100.00%)	0 / 1 (0.00%)

General disorders and administration site conditions Temperature intolerance subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 1 (0.00%) 0	0 / 1 (0.00%) 0
Reproductive system and breast disorders Dysmenorrhoea subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	0 / 1 (0.00%) 0	0 / 1 (0.00%) 0
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) Nervousness subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0 0 / 3 (0.00%) 0	0 / 1 (0.00%) 0 1 / 1 (100.00%) 1	0 / 1 (0.00%) 0 0 / 1 (0.00%) 0
Investigations Blood pressure increased subjects affected / exposed occurrences (all) Aspartate aminotransferase increased subjects affected / exposed occurrences (all) Hepatic enzyme increased subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0 0 / 3 (0.00%) 0 0 / 3 (0.00%) 0	0 / 1 (0.00%) 0 0 / 1 (0.00%) 0 1 / 1 (100.00%) 1	0 / 1 (0.00%) 0 0 / 1 (0.00%) 0 0 / 1 (0.00%) 0
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Migraine subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0 0 / 3 (0.00%) 0 0 / 3 (0.00%) 0	1 / 1 (100.00%) 1 0 / 1 (0.00%) 0 0 / 1 (0.00%) 0	0 / 1 (0.00%) 0 0 / 1 (0.00%) 0 0 / 1 (0.00%) 0
Ear and labyrinth disorders			

Ear pain subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 1 (0.00%) 0	0 / 1 (0.00%) 0
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) Dry mouth subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0 0 / 3 (0.00%) 0	0 / 1 (0.00%) 0 0 / 1 (0.00%) 0	0 / 1 (0.00%) 0 0 / 1 (0.00%) 0
Hepatobiliary disorders Hepatic steatosis subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 1 (0.00%) 0	0 / 1 (0.00%) 0
Skin and subcutaneous tissue disorders Urticaria subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 1 (0.00%) 0	0 / 1 (0.00%) 0
Renal and urinary disorders Pollakiuria subjects affected / exposed occurrences (all) Micturition urgency subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0 0 / 3 (0.00%) 0	0 / 1 (0.00%) 0 0 / 1 (0.00%) 0	0 / 1 (0.00%) 0 0 / 1 (0.00%) 0
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0 0 / 3 (0.00%) 0	0 / 1 (0.00%) 0 0 / 1 (0.00%) 0	0 / 1 (0.00%) 0 0 / 1 (0.00%) 0
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Upper respiratory tract infection	0 / 3 (0.00%) 0 	0 / 1 (0.00%) 0 	0 / 1 (0.00%) 0

subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 1 (0.00%) 0	0 / 1 (0.00%) 0
Oral herpes subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 1 (0.00%) 0	0 / 1 (0.00%) 0
Conjunctivitis subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 1 (0.00%) 0	0 / 1 (0.00%) 0
Metabolism and nutrition disorders Vitamin D deficiency subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 1 (0.00%) 0	0 / 1 (0.00%) 0
Diabetes mellitus subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 1 (0.00%) 0	0 / 1 (0.00%) 0

Non-serious adverse events	Period 2: TAK-994 30 mg BID		
Total subjects affected by non-serious adverse events subjects affected / exposed	0 / 3 (0.00%)		
General disorders and administration site conditions Temperature intolerance subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Reproductive system and breast disorders Dysmenorrhoea subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Nervousness subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Investigations			

Blood pressure increased subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Hepatic enzyme increased subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Migraine subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0 0 / 3 (0.00%) 0 0 / 3 (0.00%) 0		
Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) Dry mouth subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0 0 / 3 (0.00%) 0		
Hepatobiliary disorders Hepatic steatosis subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Skin and subcutaneous tissue disorders			

Urticaria subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Renal and urinary disorders Pollakiuria subjects affected / exposed occurrences (all) Micturition urgency subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0 0 / 3 (0.00%) 0		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0 0 / 3 (0.00%) 0		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) Oral herpes subjects affected / exposed occurrences (all) Conjunctivitis subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0 0 / 3 (0.00%) 0 0 / 3 (0.00%) 0 0 / 3 (0.00%) 0		
Metabolism and nutrition disorders Vitamin D deficiency subjects affected / exposed occurrences (all) Diabetes mellitus	0 / 3 (0.00%) 0		

subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 July 2021	The following changes were implemented as per Amendment 1: 1. The duration of the randomized withdrawal period was shortened from 4 to 2 weeks. 2. An open-label extension period was added to evaluate safety of the TAK-994 regimen following the randomized withdrawal period. 3. An objective and endpoint related to microsleeps was added. 4. Low, middle, and high doses information was added to the protocol. 5. Ambulatory blood pressure monitoring and guidance was added. 6. Karolinska Sleepiness Scale and Narcolepsy Severity Scale for Clinical Trials scales have been added to the objectives and endpoints. 7. The possibility for participants to roll over to an optional open-label extension study was added to the study design. 8. The number of sites estimated to be included was updated from 70 to 81. 9. Stratification by Epworth Sleepiness Scale total score (<10 , ≥ 10) and total number of cataplexy episodes in the last 7 days (≤ 3 , >3) was added for the randomized withdrawal period. 10. The study title was updated. 11. The Overactive Bladder Questionnaire – Long Form (OAB-q-LF) and Patient Perception of Bladder Control (PPBC) have been added to objectives and endpoints. 12. The overnight stay at Day 56 to monitor possible withdrawal effect was replaced by a telephone call 24 hours after the last dose in the active drug extension period. As a result, pharmacokinetics (PK) and renin/aldosterone samples to be taken before discharge will be taken at Day 56 rather than 57.
08 July 2021	The following changes were implemented as per Amendment 1: 13. The clinical study experience and benefit-risk information was updated with the most recent information. 14. Open-label wording was removed from the figure on study design schematics. 15. The Columbia Suicide Severity Assessment scale was added at each visit. 16. The threshold for Maintenance of Wakefulness Test (MWT) was corrected to 7 minutes. 17. Statements with regard to the need to consult the sponsor and/or designee before the initiation of any concomitant medication was removed. 18. The excluded medications were updated to differentiate between prior use of medications resulting in exclusion and prior use of medications resulting in exclusion at the discretion of the investigator. 19. Relaxation of study restrictions due to the long duration of this study. 20. The instruction that breakfast and lunch should be standard meals each containing approximately 30% fat (relative total calories) was removed. 21. A partially unblinded safety physician, separate from the study team, was added. 22. Addition to include available information on coronavirus disease 2019 (COVID-19) vaccination. 23. Orthostatic blood pressure measuring was added. 24. A physical examination was added at Baseline 2. 25. Update to have PK samples close to MWT measurement for the potential PK/pharmacodynamic analysis. 26. The planned pregnancy test on Day 55 was moved to Day 56. 27. It was updated that pregnancy avoidance counselling should continue through follow-up. 28. An additional pregnancy test 30 days after the last intake of study drug was added.
23 September 2021	The following changes were implemented as per Amendment 2: 1. It was clarified that liver function test results should be available to check participant eligibility before enrollment. 2. Glutamate dehydrogenase (GLDH) and fluoride assessments have been added. 3. Additional safety assessments were added at increased frequency. 4. A criterion was added to assess participant suitability based on blood pressure data. 5. Orthostatic blood pressure measurement was added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
03 November 2021	A safety signal has emerged in Phase 2 studies of TAK-994. As an immediate precautionary measure, Takeda has suspended dosing of patients and has decided to stop Phase 2 studies early.	-

Notes:

Limitations and caveats

None reported